**Summary Minutes of the Computational Toxicology Framework Consultation Panel Meeting**
**September 12, 2003, Marriott Metro Center, Washington D.C.**

Panel Members: See Panel Roster – Attachment A.
Date and Time: Friday, September 12, 9:00 A.M. – 4:00 P.M.
Location: Marriott DC Hotel at Metro Center, 775 12th Street, N.W., Washington, DC.

Purpose: The purpose of this meeting was for the Panel to be briefed by the Agency, hear public comments, and conduct a consultation with the Agency on its Computational Toxicology Framework.

Attendees:

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| Chair: | Dr. George W. Lucier |
| Panel Members: | Dr. Melvin Andersen<br>Dr. John Balbus<br>Dr. Richard Becker<br>Ms. Patricia Billig<br>Dr. Stuart Cagen<br>Mr. Harvey Clewell<br>Dr. Darrell Donahue<br>Dr. B. Alex Merrick<br>Dr. Charles A. Pittinger<br>Dr. Clifford P. Weisel<br>Dr. Angela Wilson<br>Dr. Andrew Worth |
| EPA SAB Staff: | Dr. James Rowe, DFO<br>Dr. Vanessa Vu, SAB Staff Office Director |

Others attending:

Tom Barnwell, EPA/ORD/NCER
Elizabeth Cho-Ferlick, Thomas Jefferson University
Elaine Francis, EPA/ORD/NCER
William Glaze, SAB EC Chair
Karen Hammerstrom, EPA/ORD/NCEA
Robert Kavlock, EPA/ORD/NHEERL
Steven Kueberuwa, EPA/OW/OST
John Liccione, EPA/OPP/HED
Alberto Protzel, EPA/OPP/HED
Lawrence W. Reiter, EPA/ORD/NHEERL
Phil Sayre, EPA/SABSO
Pat Schmieder, EPA/ORD/NHEERL

Sue Shallal, EPA/SABSO
Greg Toth, EPA/ORD/NERL
Eric Weber, EPA/ORD/NERL
Douglas Young, EPA/ORD/NRMRL
Phil Zahodikin, CRC Press

## Meeting Summary

The discussion generally followed the issues and general timing as presented in the meeting Agenda (Attachment B). The meeting began at 9:00 A.M. and lasted until 3:55 P.M. on Friday, September 12, 2003.

## Introductory Remarks and Welcome

Dr. James Rowe, Designated Federal Officer (DFO) for the Computational Toxicology Framework Consultation Panel (CTF) opened the meeting and stated that its purpose is for the *ad-hoc* Science Advisory Board (SAB) panel to consult on the Framework with EPA's Office of Research and Development (ORD). This panel was formed in accordance with the procedures outlined by the Federal Advisory Committee Act (FACA). Since today's meeting is a consultation, no formal report will be prepared, though both minutes and a transcript will be recorded, and will be available one month after the meeting.

FACA panel formation guidelines require that potential conflicts of interest or appearance of impartiality be considered. Each committee member was therefore required to submit confidential financial disclosure information. This information was reviewed by the SAB Ethics and FACA officer, who determined that no conflicts of interest exist, and that the potential for appearance of lack of impartiality is low. Biosketches for each of the panel members are posted on the SAB website and were also available as a handout during the meeting (Attachment A).

Dr. Rowe then asked the panel and audience to introduce themselves, and briefly reviewed the day's agenda.

## Remarks by the SAB Staff Office Director

Dr. Vanessa Vu, SAB Staff Office Director, welcomed participants to the meeting and thanked the panel, Agency representatives, and DFO, for their time and advice. She also introduced Dr. William Glaze, SAB Executive Committee (EC) Chair, who attended the meeting.

Introduction of the Topic

Dr. George Lucier, Panel Chair, reiterated that the panel would be conducting a consultation to provide the Agency with advice on the Framework. The product of the meeting will be a collection of the panel members' individual views and comments. Seven charge questions (listed on the Agenda, Attachment B) were provided by the Agency to focus the panel's discussion.

An overview of the Framework would be presented first, by members of the Agency writing team. The panel would then discuss eight major topics identified in the document. Dr. Lucier asked that panel members identify any major suggestions or recommendations they may have.

Background and Purpose for Computational Toxicology Research Framework

**Computational Toxicology Overview**
*Lawrence W. Reiter, Ph.D., ORD/NHEERL*

Dr. Reiter introduced his presentation by stating that the Framework was intended to be used both by ORD to implement a research program, and as a means of communicating the Agency's research needs in the area of computational toxicology. ORD is asking the panel to review this framework and provide its advice on how such research should be prioritized as ORD begins to shape a research program.

The Agency's Science Policy Council (SPC) developed an interim policy and an action plan two years ago on the use of genomics technology and information within the Agency. The potential of genomics research was recognized as a powerful tool for understanding the molecular basis of toxicity and developing biomarkers, and the Agency supported continued research. However, it was decided that genomics data alone were insufficient as a basis for risk assessment and management decisions. The interim policy recommended limited use of such data while the Agency gains experience in assessing their quality, accuracy and reproducibility. Genomics data were thought to be useful in a weight-of-evidence approach for human health and ecological risk assessments.

The interim EPA genomics policy is posted at:
http://www.epa.gov/osp/spc/genomics.htm

Dr. Reiter then presented a flow diagram illustrating the sequential steps in quantitative risk assessment. EPA research includes the development of methods to detect, characterize, and evaluate single chemicals individually. However, prioritization has proven a challenge: many priority lists exist, compiled by different authorities, and data are lacking to reduce uncertainties.

In addition to determining which chemicals are priorities, numerous scientific challenges exist. Information is lacking on delineating toxicity pathways and extending cross- and within-species extrapolations, and endpoints for Quantitative Structure Activity Relationships (QSAR) models need to be identified. Further knowledge is needed on exposure biomarkers, fate and transport models, and dose metrics; and a better understanding of cross- and within-species variations in pharmacokinetics is crucial.

Genomics, combined with computational methods and bioinformatics, can be used to integrate modern computing and information technology with molecular biology and chemistry, and help improve EPA's prioritization of data requirements and risk assessments for toxic chemicals.

**Computational Toxicology Briefing for the SAB**
*Robert Kavlock, Ph.D., ORD/NHEER*

Dr. Kavlock, Chair of the Framework Writing Team, presented background information on the computational toxicology efforts at EPA. Under the leadership of Dr. Paul Gilman, Science Advisor to the Agency and Assistant Administrator of ORD, emphasis on computational toxicology has increased in recent years. As part of these efforts a technical design team was formed in 2002 and included representatives from all five ORD laboratories and centers. The group was charged with drafting a Framework for a computational toxicology research initiative within ORD. In addition, the development of a research strategy in computational toxicology was identified as an Annual Performance Measure for FY04.

Dr. Kavlock outlined the overarching themes in the Framework and listed its three main objectives:

1. Improve linkages in the source-to-outcome paradigm;
2. Provide predictive models for screening and testing; and
3. Enhance quantitative risk assessment.

He then presented a diagram illustrating the source-to-outcome continuum, as described in the Framework document and listed linkages from source to outcome, including: chemical transformation and metabolism; diagnostic/prognostic molecular indicators; dose metrics; characterization of toxicity pathways; metabonomics; and systems biology.

Predictive models for screening and testing (the second objective of the Framework) include QSAR approaches, pollution prevention strategies, and high-throughput screening. The third objective, enhancing quantitative risk assessment, can be accomplished through the application of computational methods, dose response assessments, cross species extrapolations, and taking into account chemical mixtures.

Proof of concept studies are currently being conducted by ORD using endocrine disrupting chemicals (EDCs), including research on receptor binding models, thyroid

hormone pathways, steroidogenesis, and the hypothalamic-pituitary axis. Other activities will include infrastructure building and partnership development, and Science to Achieve Results (STAR) Requests for Assistance (RFAs) for related research. Today's SAB consult will be followed by a workshop, scheduled September 29-30, 2003, to introduce the Framework and discuss research strategies and approaches with other organizations. The workshop will also serve to communicate the Agency's regulatory needs.

Comments and input from both the SAB consult and workshop will be reviewed and incorporated into an updated version of the Framework, and further activities will be coordinated with the EPA Genomics Task Force. The Framework writing team will evolve to become an implementation team, responsible for identifying specific areas for program development. Budget resources have been allocated or redirected for FY04 and FY05; the STAR program will also be used to complement intramural programs with additional outside research. Performance measures will include both research outputs (such as libraries of toxicity pathways) and programmatic outputs, such as predictive models to prioritize chemicals or improved efficiency in risk assessment.

Following the presentations, Dr. Lucier commented that he was pleased to see an emphasis on integrating research across ORD, stating that such coordination has not frequently been the case in the past.

Panel members commented that the Framework itself does not include a discussion on budget for this effort, or on how the budget would be managed. Dr. Reiter explained that, although major budget increments are expected in FY04 and FY05, it is difficult at this time to plan beyond that.

Discussion of Science Areas Relevant to Computational Toxicology/Charge Questions

***NOTE: General discussion on each topic is included in this section. Specific recommendations by the panel are included in the following section (Summation of Panel Recommendations) under the appropriate charge question.***

**Biological Modeling/Systems Biology**
*Lead Discussant: Dr. Melvin Andersen*

Dr. Andersen presented background information on systems biology in a computational framework Although systems biology is not a new area, it needs to be more clearly defined. Biologically-based models for simulating responses have already been developed and used. As toxicity is a biological perturbation, systems biology can be applied to determine normal pathways, and then identify how these pathways are perturbed in the presence of toxicity. Genomics technology can be used to map networks and identify pathways and their components. Although technology is not yet sufficient to model an entire cell, specific signaling pathways can already be determined. Whether pathways with toxic perturbations can be identified from these depends on data acquisition, but is theoretically possible using genomic technologies (e.g., microarrays).

Systems biology models are the natural descendants of biologically-based dose response (BBDR) models, and reflect new structures for thinking about toxicity cascades. Although there are not currently sufficient data to develop these models, such data are likely to become available in the near future. The Framework has started to outline tools for integrating aspects of toxicity in biological systems.

**Mathematical Biology/Mathematical Chemistry**
*Lead Discussant: Dr. Angela Wilson*

Dr. Angela Wilson provided several comments and suggestions in the area of mathematical biology and chemistry. Her recommendations, along with those from other panel members, are listed in the next section under the appropriate charge questions.

**Genomics/Metabonomics**
*Lead Discussant: Dr. B. Alex Merrick*

Dr. Merrick presented information on toxicogenomics and the development of the Chemical Effects in Biological Systems (CEBS) database. Toxicogenomics is the study of the response of a genome to environmental stressors and toxicants. Identification of such stressors and toxics may involve analysis of several such compounds from a chemical mixture. Proteomics involves the identification of proteins, using gels, isolation, digestion, and amplification. Metabonomics takes this concept a step further, providing the ability to describe a system by measuring changes that occur in a global manner, and by recreating toxicity pathways. A good toxicological characterization is crucial to the eventual identification of markers. The CEBS database was created to provide such toxicological information, and was launched about two weeks ago (August 2003). The database will later include information on RNA and protein, and will soon be available to the public.

**Computational Biology**
*Lead Discussant: Dr. Andrew Worth*

Dr. Worth provided comments and suggestions in the area of computational biology. His recommendations, along with those from other panel members, are listed in the next section under the appropriate charge questions.

**Dose Metrics**
*Lead Discussant: Dr. Clifford P. Weisel*

Dr. Weisel explained that the basic concept of dose metrics is to understand the relationship between dose and response. Physiological data are necessary to understand this relationship but not always available; information on metabolism is also needed, and should be chemical-specific. Potential biomarkers of exposure are promising, but need to

be validated before they can be used reliably. Exposure data are also important; fate and transport models are not necessarily exposure models. Parameters such as age and food chain level must be taken into account to estimate exposure at the population and ecosystem levels. A more direct way of estimating exposure is by using health-based indicators and endpoints rather than environmental standards (e.g., ambient air quality).

**Human Risk Assessment**
*Lead Discussant: Dr. John Balbus*

Dr. Balbus provided comments and suggestions in the area of human risk assessment. His recommendations, along with those from other panel members, are listed in the next section under the appropriate charge questions.

**Ecological Risk Assessment**
*Lead Discussant: Dr. Charles A. Pittinger*

Dr. Pittinger began by defining the concept of computational toxicology, using mathematical and computational models for predicting effects and understanding mechanisms. Applying this to an ecological scale requires taking into account all aspects of an ecosystem, from sub-cellular processes to populations and ecosystems.

As the focus of this framework is on the "omics" research, rather than on the more conventional QSAR models, it may prove difficult to assess risks and effects across the continuum of an ecosystem. It is not yet known whether a gene or protein can affect or alter an entire ecosystem. Other considerations include deciding on the criteria for applying "omics", and on what uncertainties can be considered acceptable.

An immediate gain for the practice of ecological risk assessment could be realized from ORD's computational toxicology research program, however, if some of the common eco tox test species, for which we have large amounts of standard toxicity testing, were selected for "omics" research.

**Endocrine Disruptors / Proof of Concept**
*Lead Discussant: Dr. Stuart Cagen*

Dr. Cagen stated that the framework was an important and valuable plan given that EPA must continue to be a legitimate player in the development and application of new tools. Endocrine disruptors are a reasonable choice for proof of concept, as the topic builds on current EPA leadership and can help the understanding of EDC issues.

Summation of Panel Recommendations for the Framework

***Charge Question 1:***
*Please comment on the soundness of the general organizing principles contained in the "Framework for a Computational Toxicology Research Program in ORD," including the goals of the computational toxicology program, the research needs and applications of computational toxicology, the current activities, and the proposed next steps.*

The overall impression of the panel was that the document was a good effort by a broad range of EPA scientists and should prove a useful tool for furthering EPA's mission. The panel endorsed EPA's activities in this regard, recognizing that one document cannot "do it all." The Panel further recognizes that the EPA cannot do it all with regard to computational toxicology research in the environmental area. Partnering with other agencies on fundamental biology issues relevant to creating the scientific foundation for systems biology and molecular pathways applications to computational toxicology are essential.

It would be helpful, for the overall soundness of organization, for research needs to be separated from specific tools.

It was suggested that the document should identify technologies that are ready to be applied to biological system models, as opposed to those still in developmental stages.

One shortcoming of the framework is an apparent separation from the policy section of the Agency, particularly as EPA is moving toward integration across ORD and programs or regions. This separation leads to little discussion of ethical issues, stakeholder involvement, or broader policy aims. Future frameworks should take into account issues of importance to the programs/regions, such as the involvement of stakeholders.

Given that EPA serves some public health role, the prioritization scheme in the framework should include some mention of public health goals.

The contributions of QSAR and fate and transport models are not immediately apparent from the discussion in the framework.

The section on proposed next steps is too short, and not very helpful; next steps should involve not only ORD, but other parts of EPA as well as other agencies.

Development of a research strategy is a logical step to take after the workshop. The panel urged EPA to take a broad look at the research strategy relative to its mission, rather that focusing on its specific levels of expertise.

The goals of the computational toxicology program need to consider the extent to which exposure and fate transport are involved. Proposed activities could be expanded to cite some of the recent research on exposure.

Proposed next steps should include some common research protocols, test species, and chemicals that would fill some immediate information needs in current practice of risk assessment and that would allow for some synergy and comparability between the many types of research conducted.

The appendix does not include any activities under systems biology; some of the computational biology activities should be added to that section, even if that means they will be listed under both sections.

***Charge Question 2:***
*The scope of the program (Section II) has been developed along the key activities of improving the linkages in the Source-to-Outcome Continuum, providing predictive models for hazard identification, and enhancing quantitative risk assessment. Does the panel agree that these are the major issues of concern for improving the Agency's scientific assessments of pollutants on human health and the environment, and that the needs have been clearly articulated in terms of the benefits of a computational toxicology approach? Does the Framework capture the key scientific uncertainties that need to be addressed in computational toxicology?*

The panel agreed that the answer is yes, with a few exceptions, most notably the lack of adequate coverage of exposure, and the fact that it is not linked to the source-to-outcome continuum.

The panel thought it was important to stress the risk assessment focus that systems biology has to have in an agency like the EPA. Knowledge of the biological system is often the limiting factor in understanding a system.

Understanding transfer processes (e.g., calcium or magnesium channels) is crucial to understanding systems biology. Specifically, one of the fundamental elements of understanding toxicity is knowing exactly what controls the uptake of a toxic substance into a cell.

An additional source of uncertainty in risk assessment is the series of steps in a toxic pathway that occur after the cellular dose. Mercury was cited as an example: a lot is known about mercury toxicity, but not what causes the cellular response.

Emphasis on the toxicity pathway, and understanding pathways and integrating with cellular response, are both crucial uncertainties. Both topics should be basic research components of this program.

Using language that allows flexibility, especially where there are a lot of uncertainties or missing knowledge, may make it easier to incorporate new information in future risk assessments.

The accuracy of descriptors when using QSAR, and whether they have been adequately validated, can be a concern, particularly if the goal is for computational toxicology to replace laboratory testing on animals. Descriptors should be fine-tuned, so that QSAR models give consistent answers, and probabilistic assessments will likely be needed to manage uncertainties. A validation method may need to be developed, as well as an approach to deal with outliers. Outliers can sometimes be driving a network connection or triggering an additional pathway, pointing to a important part of the network that may not have been considered. Looking at the distribution of outliers can be helpful in determining whether outliers are what they seem, and not the result of a mistake or artifact. It was also noted that any validation methods would likely differ depending on whether they would apply to commercial or public domain models.

The source-to-outcome continuum seems to focus too much on the "big picture"; understanding is also needed at the molecular level (molecular pathways).

Although the Framework mentions the importance of improving accuracy and speed, from a computational perspective, these two attributes do not always go "hand in hand."

The topic of additive variability should be considered, since computational toxicology has the effect of integrating various approaches. It was suggested that ORD involve some statisticians or mathematicians to consider how to handle this issue. One possible solution may be to place bounds on variability at each step.

A plan or framework is needed for validating each model that may be used.

Uncertainty exists in estimating actual tissue exposure to a chemical from the dose given, making the interpretation of quantitative data difficult. The interface between this information and its application in dose response assessment should be explained in more detail.

Panel members were concerned there may be too narrow a focus on reducing uncertainty. Particularly in the area of human health risk assessment, reducing uncertainty should not be limited to eliminating uncertainty factors. Efforts should also be undertaken to reduce ignorance (meaning lack of study and therefore awareness of the full range of potential health effects, especially non-cancer endpoints) and to fully characterize variability, thereby reducing overall uncertainty.

EPA should be praised for especially incorporating computational toxicology approaches to address chemical mixtures in a risk assessment setting.

The framework should more adequately describe the link between human and ecological health.

***Charge Question 3:***
*Please provide specific recommendations, where appropriate, for addressing issues that are not captured by the Framework*

The panel commented on the need for the various federal agencies to conduct complimentary, rather than redundant work, recognizing that this is a science management issue across EPA and the other agencies.

Panel members felt that environmental fate transport models are important to the program offices, and expressed hope that, in the course of deliberating a new research approach, there will be room to maintain, update, and support these models currently in use.

Children's health, and the linkages with children's exposure as part of exposure modeling should be included as part of the section on dose metrics. The Panel further recommended that the area of children's health be considered more broadly and possibly be a priority for EPA consideration (perhaps included in Section 4); the models and parameters included should be examined as to their relevance to children.

A clear definition of an adverse event should be given, as there is a considerable range of different outcomes.

In the area of human risk assessment, the harmonization of cancer and non-cancer endpoints should be considered. Although a current project to address this is listed in the Appendix, the issue should be discussed in the framework itself.

If possible, trends should be established to link all scales (biological organization, temporal and spatial) over the next 20 years.

Additional specific examples should be added in the section of ecological risk assessment. Such examples would, ideally, highlight the different challenges inherent in ecological versus human risk assessment.

Molecular epidemiology should be specifically incorporated into the framework.

The ethical implications of characterizing sensitive subpopulations should be taken into account.

Statistical approaches should be considered to address the numerous uncertainties, integrating them whenever possible.

Building on its previous work, EPA could play a key role in addressing Computational Toxicology of mixtures and this might be a candidate for priority research needs.

***Charge Question 4:***
*Can the Science Advisory Board suggest priorities within the research needs and applications of computational toxicology to environmental problems?*

EPA should work with other agencies on issues relevant to genomics and proteomics. Metabonomics, however, presents an opportunity for the Agency to play a leading role.

Translational research needs to be prioritized, with emphasis placed on translating fundamental biological knowledge into the risk assessment arena.

Projects that allow characterization of a chemical's full range of toxicity should be given a high priority. For example, many of the common chemicals that risk assessors need to address have limited toxicity data. "Omics" research could substantially improve the overall understanding of the toxic mechanisms of these chemicals and, thus, allow greater use of these chemicals in validating QSAR models for use in evaluating new or unknown chemicals.

Applications should be identified and prioritized for the short-term, as well as the long-term.

Development of an internet or modeling server should be one of the top priorities, so that maximum value can be derived from the data; another is creating a guide for validating the models (e.g., QSAR).

***Charge Question 5:***
*Establishment of an effective research program will require partnerships with outside organizations. Some of the current activities are listed in the Section III.C. Please comment on whether sufficient measures are being taken to involve the larger scientific community and the public.*

Overall, panel members were pleased that EPA is entering into partnership with other agencies with experience in computational sciences. Some examples were OW, OAR, the programs, and regions within EPA; and NTP and CDC, as other federal agencies.

However, EPA should not try to compete with basic scientists at the NIH and in academia in the generation of toxicogenomics data with the exception that metabonomic research is appropriate for EPA. Instead, EPA should focus on the translation of toxicogenomics into computational models that improve risk assessments by better defining dose response relationships, assessments of interindividual variation, hazard identification and the selection of appropriate models for use in risk assessment. In other words, EPA needs to use basic research to improve risk assessment models but they should not expected to generate the basic research.

In order to conduct sound translational research, EPA needs to foster collaborations with basic scientists at all stages of research not just at the end of those basic studies. This will help insure that EPA needs in computational toxicology are being met.

EPA may consider collaborating with the international community; Canada and Europe were specifically mentioned.

It was suggested that EPA use the planned workshop in September to hold small group discussions on specific topics brought up by the panel. In addition, risk assessment practitioners should be brought in to provide insight on how the new technologies could be used, both in the short- and long-term.

Panel members commented that a lot of planning may be required to bring about collaboration. A reasonable next step may be mapping out this effort in such a way that stakeholder input can be obtained while it can still be incorporated and funded.

***Charge Question 6:***
*The process for developing the program in computational toxicology in ORD is outlined in Section I. Please comment on whether the proposed next steps allow for the scientific issues to be addressed adequately in a timely fashion.*

In computational chemistry, a long history exists of obtaining the "right answer for the wrong reason." As this framework will establish the Agency's research directions for the next five to eight years, some discussion could be included on how the agency will be able to access more accurate modeling techniques in the future.

***Charge Question 7:***
*Please comment on whether there are any additional actions, within the context of computational toxicology as defined in the Framework that could improve the Agency's scientific assessments of chemical hazards to human health and the environment.*

It was suggested that ORD take a step back from its current approach to look at the "total patient", i.e., begin with the effect and determine cause, as is frequently done in microbial risk assessment. ORD could do this by using RFPs to look into the development of a patient system, such as the systems used by pharmaceutical companies.

More access to available data should be established, focusing on a priority list of chemicals.

The high-throughput and high-context nature of computational toxicology are one of its advantages; the power of this technology can be used to look at multiple endpoints. The key challenges for ORD will be to ensure that the various research projects undertaken have a reasonable degree of complementarity in terms of chemicals evaluated and test organisms. "Omics" research could answer some key questions about chemicals

commonly encountered by risk assessors as well as provide needed guidance on addressing unknown chemicals, if ORD has a strategy from the beginning to maximize the benefits of research dollars spent by structuring the overall research program to be internally comparable and to complement current toxicity information and needs regarding specific chemicals and test organisms.

Public Comments

Eric Webber (ORD), a member of the framework writing team, asked to address the panel and thanked panel members for their comments. He then addressed some comments that were given throughout the discussion. ORD is working with OPPT on environmental fate and transport, specifically on expanding the EPI suite. Regarding chemical mixtures, Dr. Webber explained that EPA management supports moving forward with a new effort. In metabonomics, a new instrument has been purchased and a new GS15 position has been approved for an expert in the field; the panel's assistance would be valuable in identifying suitable candidates. Finally, the team is aware that program offices need software tools that are easy to use; work is in progress to develop models that run on the Windows platform.

Meeting Conclusion

At the conclusion of the discussion, the Chair thanked the panel members and EPA participants. The DFO thanked the panel as well, and adjourned the meeting at 3:55pm.

**Action Item:**

- Panel members who prepared presentations for today's discussion were requested to email their PowerPoint slides to Dr. Jim Rowe (see Attachment H).

Respectfully Submitted:

_____/Signed/_____

James N. Rowe, Ph.D.
Designated Federal Officer

Certified as True:

_____/Signed/_____

George W. Lucier, Ph.D.
CTF Panel Chair

## ATTACHMENTS

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| Attachment A: | Roster and Biosketches of the CTF Panel |
| Attachment B: | Meeting Agenda (including Charge Questions) |
| Attachment C: | Federal Register Notice |
| Attachment D: | Participant Sign-In Sheet |
| Attachment E: | Draft Framework for a Computational Toxicology Research Program in ORD |
| Attachment F: | Reiter presentation: Computational Toxicology Overview |
| Attachment G: | Kavlock presentation: SAB Briefing on Computational Toxicology Framework |
| Attachment H: | Individual Panel Member Presentations |